



PROSPECTS OF MOLECULAR GENETICS IN SPORTS MEDICINE

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ABSTRACT

During the last two decades, sports medicine is increased and experienced a stage of rapid development, especially in such areas as the study of strength, endurance, sports injuries and psychology. Study of ongoing changes when performing exercises at the cellular and molecular levels led to the development of new areas in the sports science as known as genetic medicine that deals with the genetic basis of athletic phenotype. Around 66 % of the variance in athlete status is explained by genetic factors, the remaining variance is due to other factors such as training, nutrition, equipment, motivation, sleeping and epigenetics. Over the last two decades, at least 155 genetic markers (located in almost all chromosomes and mtDNA) were associated with elite athlete status (93 genetic markers with endurance and 62 markers with power/force). The number of identified genetic markers associated with sports activity, grew at a rate exponentially: in 1997 – 5 genes; in 2000 – 24 genes; in 2004 – 101 genes. During the last 19 years, found that at least 120 of genetic markers associated with elite athlete status (77 genetic markers related to endurance and 43 genetic marker settings capacity/power). Of the polymorphisms associated with sports endurance, the angiotensin-converting enzyme (ACE) and alpha actinin-3 (ACTN3) polymorphisms have been the most frequently studied, and meta-analyses have confirmed the associations. ACTN3 is absent in approximately 18% of European population, 25-29% of Japanese population and overall about 1.5 billion people in all countries. Therefore, to date, available genetic tests based on small sample sizes and the selected analytical methodology can lead to erroneous associations and to reassess the size of the effect, and of course, the use of such limited data does not allow us to predict athletic ability with high accuracy.

Keywords: Sports medicine, Elite athletes, Genotype, PPARA, ACTN3, SNPs.

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1. HAS ATHLETIC PERFORMANCE REACHED ITS PEAK?

During the last two decades, sports medicine is increased and experienced a stage of rapid development, especially in such areas as the study of strength, endurance, sports injuries and psychology [1]. Athlete preparation, conditioning, including physical training, nutrition, and medicine, was affected by technological improvements and innovations in the twentieth century. In this connection, Fogel [2] coined the term "techno-physiological evolution" to describe anthropometric gains of athletes' body. However, the most noticeable parameters affect the quality of sport, relate to biology, including genetics [3-5]: the physiological processes (especially time-dependent processes such as growth and aging [6-8] and environment [9, 10] which can be either natural (e.g. ambient temperature, gas content, barometric pressure, winds, etc.) or artificial (human) based on the cultural [11] and technological [12] contexts.

2. WHAT IS THE ROLE OF GENETIC MEDICINE IN SPORT?

This study one of very few studies which have investigated of ongoing changes when performing exercises at the cellular and molecular levels led to the development of new areas in the sports science as known as genetic medicine that deals with the genetic basis of athletic phenotype [13, 14]. Understanding the genetic architecture of athletic opportunities is an important step in the development of methods for the identification of talents in sports. Genetics and interaction with the environment determine an individual's athletic ability. Around 66 % of the variance in athlete status is explained by genetic factors, the remaining variance is due to other factors such as training, nutrition, equipment, motivation, sleeping and epigenetics [13, 15]. Studies concerning molecular genetic predictors yielded a variety of potentially important markers are DNA polymorphisms that promote the propensity for success in certain types of sports.

3. GENES AND ATHLETIC PERFORMANCE

Over the last two decades, at least 155 genetic markers (located in almost all chromosomes and mtDNA) were associated with elite athlete status (93 genetic markers with endurance and 62 markers with power/force) [1]. At the same time, the number of identified genetic markers associated with sports activity, grew at a rate exponentially: in 1997 – 5 genes; in 2000 – 24 genes; in 2004 – 101 genes.

The paper's primary contribution is finding that two important aspects for athletes are endurance and strength capacities vary widely in individuals, even among well-trained athletes. In this respect, during the last 19 years, found that at least 120 of genetic markers associated with elite athlete status (77 genetic markers related to endurance and 43 genetic marker settings capacity/power) [1]. Of these genetic markers, 11 (9%) (markers of endurance: ACE 1, ACTN3 577X, PPARA rs4253778 G, PPARGC1A Gly482; markers of capacity/power: ACE D, ACTN3 Arg577, AMPD1 Gln12, HIF1A 582Ser, MTHFR rs1801131 C, NOS3 rs2070744 T, PPARG 12Ala) showed positive associations with athlete status in three or more studies and six markers (CREM rs1531550 A, DMD rs939787 T, GALNT13 rs10196189 G, NFIA-AS1 rs1572312 C, RBFOX1 rs7191721 G, TSHR rs7144481 C) were identified during the research genome-wide Association (GWAS) among African-American, Jamaican, Japanese, and Russian athletes.

Studies of genetic associations have identified several loci associated with phenotypes of physical possibilities [16]. Of the polymorphisms associated with sports endurance, the angiotensin-converting enzyme (ACE) and alpha actinin-3 (ACTN3) polymorphisms have been the most frequently studied, and meta-analyses have confirmed the associations. Angiotensin-converting enzyme gene (ACE) which had concluded that one of the polymorphic alleles of ACE gene is allele-I provides tolerance, and allele-D – speed-power qualities of athlete, on the basis of higher frequency of alleles in athletes, successful in their respective sports in relation to the control group [17]. However, in the future, a number of authors will find no differences in the frequency of occurrence of genotypes in athletes and people who are not involved in sports [18, 19]. Nevertheless, differences will be appeared in the analysis of the study in athletes' genotypes, specializing in several sport fields [20]. For example, swimmers were discovered the increased frequency of occurrence of I-allele and decreased a frequency of D-allele; in athletes these were involved in rowing, marathon swimming, and triathletes, on the contrary, the frequency of I-allele reduced, but the frequency of D-allele were increased. Therefore, the observed differences were expressed stronger in elite athletes compared to skilled.

Several single studies assessing sports endurance have focused on the peroxisome proliferator activated receptor alpha gene (*PPARA*); nevertheless, the results have been inconsistent, possibly due to small sample sizes.

One of the most profound studies have been carried out in respect of only nucleotide polymorphism (SNP) ACTNs (actin-binding proteins) are the primary structural components of Z - lines in skeletal muscle [21]. There

are two protein isoforms of α -actinin (α -actinin-2 (ACTN2) and α -actinin-3 (ACTN3), which differ in localization in muscle fibers [22, 23]. ACTN3 is expressed only in skeletal muscle fibers which contraction is quick [23]. It is important to make a complex of actin-miosin and plays a regulatory role in the coordination of contraction of muscle fibers.

ACTN3 is absent in approximately 18% of European population, 25-29% of Japanese population and overall about 1.5 billion people in all countries. These individuals are homozygous for the alleles coding a premature stop codon in the R577X (rs1815739, the transition C-to-T at nucleotide position 1729 in open reading frame ACTN3) [23, 24]. Muscles pathology of these people is not observed, since α -actinin-2 compensates for its absence in muscle fibers which contraction is rapid.

For the first time, Yang, et al. [25] suggested that the RR and RX genotypes of ACTN3 associated with a speed-power sport, whereas the XX genotype is associated with the manifestation of endurance of the Australian athletes because the latter is not observed in elite athletes speed-strength sports involved in the Olympic Games. The ACTN3 R allele and RR genotype are associated with the upper level of the power orientation in athletes in a wide range of ethnic groups [24, 26]. In a meta-analysis Alfred, et al. [27] it is shown that the ACTN3 RR genotype is more common among European athletes speed and power sports than among athletes. In another meta-analysis Ma, et al. [28] also found a positive Association between the ACTN3 RR and RX genotypes and athletic status in speed-power kinds of sports, but only in European populations, but not in Asian or African. Some studies have assessed the association between ACTN3 R577X genotype and athletic status in these Asian athletes like fighters, track and field athletes [24, 29]. In operation [24] the frequency of RR and RX genotypes were positively related to the level of athletic status (that is, local < national < international for speed and power track and field sports and fighters, but not detected carriers of the XX genotype against the Olympians, like the results of Yang, et al. [25]. When looking at independent cohorts of elite athletes for endurance, the ACTN3 X allele and XX genotype was associated with the elite manifestation of endurance in some, but not all studies. Although reported that ACTN3 RR genotype is associated with the manifestation of endurance [30] the role of the ACTN3 R577X genotype in the manifestation of endurance remains unclear.

4. CAN GENOTYPE DETERMINE THE SPORTS PHENOTYPE?

There are contradictions in the results regarding the association between ACTN3 R577X genotype and sex differences in muscle phenotypes, e.g., strength and power of muscles [31, 32]. It is revealed that ACTN3 XX genotype is associated with the manifestation of endurance only female athletes [25]. While the work found a positive relationship between ACTN3 R577X genotype and the relative maximum power in WAnT Japanese men athletes but not in women. Seem to play a role as sex hormones associated with the volume and mobility of the muscles, and the absolute mass of muscles associated with differences in muscle phenotypes. Future research is needed to determine the sexual-dependent effect of ACTN3 R577X genotype in muscle phenotypes.

5. PPAR FAMILY

In recent years, active research on the family of nuclear receptors activated by proliferator peroxisome (PPAR), which athletes regulate the expression of many genes involved in lipid and carbohydrate metabolism (PPAR α , PPAR γ , PPAR δ). Some studies revealed that the PPAR family and one of their common coactivator 1 α -coactivator PPAR γ (PGC1 α) plays a critical role in the energy supply of skeletal muscles and myocardium [33-35].

Thus, the PGC1A gene is expressed primarily in heart, muscle, and adipose tissue, to a lesser extent in the liver, pancreas and brain. Polymorphism of this gene is Gly482Ser-mutation, frequency in the global population is

30-40% and is associated with a decrease in the level of gene expression and, consequently, low physical performance [36].

The PPARA gene (activator peroxisome proliferation of α -receptor) is expressed in slow muscle fibers, liver, heart, brown adipose tissue, that is, in those tissues where there is increased catabolism of fats to obtain a large output of energy products. Therefore, in muscle PPARA is expressed 7 times more than fat [37]. During exercise, aerobic nature is an increase in the use of fatty acids due to activation of PPAR α protein cascade of genes, which contributes to the improved oxidative capacity of skeletal muscle [38, 39].

The most frequently analyzed in this gene was a variant of the polymorphism located in intron 7 (G/C, rs4253778). Meta-analysis studies, case-control, conducted to assess the Association between the G/C polymorphism of the PPARA gene and sports that require endurance, showed that athletes with high ability in these sports have a higher frequency of GG genotype and allele G [40].

Association studies case-control is widely used to identify susceptibility genes, and they are still the most common design in sports genomics analysis [41]. They can determine that one allele of the polymorphism is more common in the group of elite athletes than in the General population. However, one of the greatest limitations of these types of research remains a small sample of them. However, this limitation can be overcome by performing meta-analysis, because when you combine such studies with conflicting reports about 20-30% of their number become statistically significant [42, 43].

The results of several meta-analyses have allowed establishing that the total number identified to date, genetic markers, only 31 showed positive associations with athlete status in at least 2 studies and 12 in 3 or more studies [27, 28, 34, 40]. On the other hand, the value of the 29 markers (24%) had played in at least one study that indicates a possible false-positivity of information. However, the reason for this may lie in the other.

6. REGIONAL ASPECTS OF SPORTS MEDICINE

It is now a matter of considerable interest is the fact that the athletes that dominate certain sports, come from specific geographic areas (Eastern or Western regions of Africa, South Asia) for example, marathon runners from Ethiopia or Kenya, African-American sprinters from Jamaica or the United States, gymnasts and figure skaters from Japan, Korea or China [3, 4, 11]. Although these cases are more likely to be a reflection of the historical socio-economic and cultural characteristics of each region, it is assumed that the specific place of residence insulation sports qualities based on the uneven distribution of genetic characteristics relevant to physical and metabolic properties of individuals residing in each region [44]. In this respect, it would be desirable to expand the range of genetic studies and other still poorly known regarding sports achievements of the population and regions where possible identification of new genes associated with new phenotypes (for example, the Central Asian region located at the crossroads between Caucasian, African and Asian populations, and have a pretty deep tradition and sporting success in wrestling Kurash.

Moreover, despite intensive research, while there is only a little progress in the identification of genes that are locally or widely associated with athletic qualities [33] with the exception of variants in the genes ACTN3 and ACE [19, 21, 28]. The reason for this is as follows:

Each of single-nucleotide polymorphisms (SNPs), usually has only a small functional effect, and therefore its original research ends with the development of genetic evaluation method, summing the number of alleles of the potential impact of SNPs for predicting athletic qualities [14, 21] reactions to training [13, 20] or risk of obesity, hyperlipidemia or hyperglycemia in relation to physical fitness [45]. Genetic evaluation method usually shows the distribution among Caucasian populations and although the best estimate of the athletes above, their extreme qualities cannot be reasonably explained by the summation of common SNPs with small effects [46]. According to

recent literature data we can assume that rare and extreme phenotypes of elite athletes are based on rare functional changes or mutations that arise and are selected fairly recently in the course of human history, as these SNPs or mutations were detected only in some global regions. This concept is quite close to the idea used to detect hereditary diseases caused by mutations in single or multiple genes [47].

The primary use in the past decades the traditional methodology of candidate genes in the genetics of sports limited success in identifying genes associated with elite athletic quality. However, in recent years, along with that began to appear some attempts to use analysis of genome-wide Association (GWAS) [15, 33, 47].

Changing preferences from the methodology of candidate genes to GWAS has resulted in the emergence of the problem of multiple comparisons, where they must overcome the threshold of the standard genome-wide values are equal for the European population by 5×10^8 for the African population of 1×10^8 [48]. If the target region is extended to include the whole genome of 3×10^9 base pairs, taking the frequency of sequence variations in our genomes - nearly 1 out of 1000 base pairs, each person should probably have 3×10^6 variations in your genome. Therefore, to identify SNP and structural variation associated with the extreme phenotype, it would be extremely difficult, even if there were hundreds or thousands of DNA samples from elite athletes. This is the main problem of sports genomics. It seems that rare SNPs are more region-specific and occurred at a later period in the history of human evolution than common SNPs.

Another view includes the notion that endurance running is a newly acquired common phenotype of all modern humans [49]. Nevertheless, remains uncertain whether to treat the extreme phenotypes of elite athletes to a limited number of rare variants to high or combinations of common variants.

To improve the effectiveness of sports genetics primarily will require analysis based on a detailed full [17, 18]. To find highly correct and repeatable variants associated with athletic phenotypes, the sample sizes for the analysis must be greatly increased. However, confirmation of the relevance and reproducibility for specific populations can be achieved and the conduct of family studies of athletes, which may facilitate the discovery of rare variants with large effect in athletic phenotypes. In the refining of sports, genetics plays an important role also assess the similarities and differences between the sexes and among ethnic groups.

Therefore, to date, available genetic tests based on small sample sizes and the selected analytical methodology can lead to erroneous associations and to reassess the size of the effect, and of course, the use of such limited data do not allow us to predict athletic ability with high accuracy. In addition, to date, most studies have focused on the study of the effect of single genes, but in the future becomes urgent need to understand the interaction of each gene with other genes and with the environment. If earlier studies that evaluate the presented genetic components of physical capacity was focused mainly on endurance and strength, future research should focus on determining the genetic markers associated with phenotypes in other sports, such as, flexibility, coordination, and temperament.

A better understanding of the sports phenotypes, related genes and their interaction with environmental factors, ultimately, will help sports doctors and trainers to identify individuals with the genetic potential of elite athletes and prone to injury and diseases.

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